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Alcohol dose in septal ablation for hypertrophic obstructive cardiomyopathy

Josef Veselka [a,*], Lothar Faber [b], Max Liebregts [c], Robert Cooper [d], Jaroslav Januska [e], Maksim Kashtanov [f], Maciej Dabrowski [g], Peter Riis Hansen [h], Hubert Seggewiss [i], Jiri Bonaventura [a], Eva Polakova [a], Eva Hansvenclova [a], Henning Bundgaard [j], Jurriën ten Berg [c], Rodney Hilton Stables [d], Jiri Jarkovsky [k], Morten Kvistholm Jensen [j]

[a] Department of Cardiology, Second Medical School, Charles University, University Hospital Motol, Prague, Czech Republic
[b] Ruhr-University Bochum, Germany
[c] Department of Cardiology, St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands
[d] Institute of Cardiovascular Medicine and Science, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom
[e] Cardiocentre Podlesí, Třinec, Czech Republic
[f] Department of Endovascular Therapy, Sverdlovsk Regional Hospital N1 and Ural Federal University, Yekaterinburg, Russian Federation
[g] Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland
[h] Department of Cardiology, Herlev and Gentofte Hospital, Hellerup, Denmark
[i] Deutsches Zentrum für Herzinsuffizienz, Universitätsklinikum Würzburg, Germany
[j] Unit for Inherited Cardiac Diseases, Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[k] Institute of Biostatistics and Analyses, Faculty of Medicine and the Faculty of Science, Masaryk University, Brno, Czech Republic

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ABSTRACT

Background: The aim of this study was to evaluate short- and long-term outcomes related to dose of alcohol administered during alcohol septal ablation (ASA) in patients with hypertrophic obstructive cardiomyopathy (HOCM). Current guidelines recommend using 1–3 mL of alcohol administered in the target septal perforator artery, but this recommendation is based more on practical experience of interventionalists rather than on systematic evidence.

Methods: We included 1448 patients and used propensity score to match patients who received a low-dose (1.0–1.9 mL) versus a high-dose (2.0–3.8 mL) of alcohol during ASA.

Results: The matched cohort analysis comprised 770 patients ($n = 385$ in both groups). There was a similar occurrence of 30-day post-procedural adverse events (13% vs. 12%; $p = 0.59$), and similar all-cause mortality rates (0.8% vs. 0.5%; $p = 1$) in the low-dose group and the high-dose group, respectively. In the long-term follow-up (5.4 ± 4.5 years), a total of 110 (14%) patients died representing 2.58 deaths and 2.64 deaths per 100 patient-years in the low dose and the high dose group (logrank, $p = 0.92$), respectively. There were no significant differences in the long-term dyspnea and left ventricular outflow gradient between the two groups. Patients treated with a low-dose of alcohol underwent more subsequent septal reduction procedures (logrank, $p = 0.04$).

Conclusions: Matched HOCM patients undergoing ASA with a low-dose (1.0–1.9 mL) or a high-dose (2.0–3.8 mL) of alcohol had similar short- and long-term outcomes. A higher rate of repeated septal reduction procedures was observed in the group treated with a low-dose of alcohol.

1. Introduction

Catheter-based therapy of HOCM was introduced 25 years ago and in the first 3 cases performed by Ulrich Sigwart the dosages of alcohol were 3 ml in one patient and 5 ml in the other two patients [1]. One of the most important trends in the continuously developing ASA technique has been a lowering of the high dose of injected alcohol used in earlier studies [2–4]. The current guidelines on hypertrophic cardiomyopathy recommend using 1–3 mL of alcohol infused into the target septal perforator artery in controlled fashion [5,6]. However, this recommendation on alcohol volume is based more on practical experience of interventionalists, rather than on strong, short- and long-term systematic evidence.

Therefore, we collected data of patients treated with ASA in nine experienced European hospital centers, and using propensity score matching analysis, we evaluated their short- and long-term outcomes with regard to procedural dose of alcohol used (1–1.9 mL vs. 2–3.8 mL).

* Corresponding author at: V úvalu 84, Prague 5, 15000, Czech Republic.
E-mail address: veselka.josef@seznam.cz (J. Veselka).

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2. Methods

2.1. Patients

A total of 1591 patients with symptomatic HOCM underwent first-time ASA between the years 1997 and 2019 and were enrolled in the Euro-ASA registry. A total of 143 (9%) patients, who previously underwent myectomy, or were treated by alcohol dose <1.0 mL or >3.8 mL, were excluded, giving a total of 1448 patients included and analyzed in this study. The study was performed in compliance with the Helsinki II declaration.

2.2. Diagnosis

The diagnosis of HOCM was established by experienced cardiologists based on typical clinical, electrocardiographic, echocardiographic, and/or cardiac magnetic resonance imaging characteristics [5,6]. All patients had a baseline LV outflow gradient ≥30 mmHg at rest, and/or ≥50 mmHg induced after provocation.

2.3. Interventions

The therapeutic decision regarding ASA was made after detailed multidisciplinary evaluation and discussions with the patients. All ASA procedures were performed by experienced interventional cardiologists, and details of the myocardial contrast echocardiography-guided ASA technique have been published in the past [7–9]; desiccated alcohol 96% was used. There were no fundamental differences in ASA technique between centers included in this study. Volume of alcohol injected was at the discretion of each interventionalist.

2.4. Study design

Patients were divided into two groups, according to alcohol dose injected (Table 1). By using propensity score (see below), patients with injected low alcohol dose of 1.0–1.9 mL were matched to comparable patients with a high alcohol dose of 2.0–3.8 mL in a ratio 1:1.

2.5. Follow-up

Demographic, electrocardiographic, echocardiographic and clinical data were recorded at baseline and during follow-up. Most patients underwent a post-procedure clinical examination three to six months after ASA and every year thereafter. The follow-up program included recording of symptoms and adverse events, physical examination, electrocardiographic, and echocardiographic examination. All clinical adverse events were confirmed by review of the medical records. The indication for repeated septal reduction therapy was at the discretion of each participating center. Assessing patient survival was done with use of the National Databases of Deaths and/or was updated by clinical communication with patients.

2.6. Outcomes

Both, short- and long-term outcomes of the matched patients in both groups were compared. We assessed (i) 30-day major cardiovascular adverse events including electrical defibrillation for VT/VF, or an appropriate ICD discharge, cardiac tamponade, and permanent pacemaker implantation; (ii) 30-day all-cause mortality rate; (iii) long-term all-cause mortality rate; (iv) long-term LV outflow gradient and

Table 1
Clinical and echocardiographic characteristics for study population at baseline and at the last check-up.

	Unmatched cohorts			Matched cohorts		
	Alcohol 1.0–1.9 mL	Alcohol 2.0–3.8 mL	*P* value	Alcohol 1.0–1.9 mL	Alcohol 2.0–3.8 mL	*P* value
	N = 465	*N* = 983		*N* = 385	*N* = 385	
Age, years	60.6 ± 12.3	56.4 ± 14.3	<0.001	59.8 ± 12.0	59.7 ± 12.8	0.918
Females, *n* (%)	262 (56)	442 (45)	<0.001	210 (55)	208 (54)	0.942
Total alcohol volume, ml (range)	1.4 ± 0.3 (1.0–1.9)	2.5 ± 0.5 (2.0–3.8)	<0.001	1.4 ± 0.3 (1.0–1.9)	2.4 ± 0.5 (2.0–3.8)	<0.001
Bundle branch block before ASA, *n*(%)	46 (10)	115 (12)	0.282	39 (10)	47 (12)	0.423
Pacemaker before ASA, n (%)	22 (5)	31 (3)	0.137	13 (3)	17 (4)	0.577
ICD before ASA, *n* (%)	22 (5)	45 (5)	0.89	18 (5)	13 (3)	0.464
NYHA class						
Baseline	2.9 ± 0.5	2.8 ± 0.5	0.004	2.9 ± 0.5	2.9 ± 0.5	0.992
Last clinical check-up	1.8 ± 0.7	1.6 ± 0.7	0.008	1.8 ± 0.7	1.7 ± 0.7	0.075
NYHA class III/IV						
Baseline, *n* (%)	389 (84)	767 (78)	0.014	325 (84)	317 (82)	0.498
Last clinical check-up, *n* (%)	65 (14)	117 (12)	0.271	55 (14)	47 (12)	0.457
Angina, CCS class						
Baseline	1.2 ± 1.2	1.1 ± 1.2	0.036	1.3 ± 1.2	1.2 ± 1.3	0.132
Last clinical check-up	0.6 ± 0.8	0.6 ± 0.8	0.215	0.6 ± 0.8	0.7 ± 0.8	0.207
LV outflow gradient at rest, mmHg						
Baseline	71.4 ± 39.6	68.7 ± 38.5	0.256	70.4 ± 39.3	70.5 ± 38.9	0.938
Last clinical check-up	16.5 ± 19.8	16.4 ± 21.9	0.618	16.6 ± 20.2	17.1 ± 23.0	0.943
>30 mmHg, *n* (%)	66 (14)	160 (16)	0.352	57 (15)	65 (17)	0.490
LV outflow gradient reduction (%)	73 ± 32	73 ± 29	0.331	73 ± 31	74 ± 26	0.871
LV end diastolic diameter, mm						
Baseline	43.0 ± 6.0	43.3 ± 6.5	0.365	43.1 ± 6.0	42.9 ± 6.4	0.925
Last clinical check-up	45.5 ± 6.2	45.5 ± 6.1	0.875	45.7 ± 6.1	45.1 ± 5.8	0.248
LV ejection fraction, %						
Baseline	71 ± 9	70 ± 9	<0.001	71 ± 9	72 ± 9	0.939
Last clinical check-up	67 ± 9	66 ± 10	0.015	67 ± 9	66 ± 10	0.426
Basal septum thickness, mm						
Baseline	19.8 ± 3.9	21.1 ± 4.4	<0.001	19.9 ± 3.8	20.0 ± 3.7	0.533
Last clinical check-up	15.2 ± 4.2	15.7 ± 4.8	0.098	15.1 ± 4.1	14.9 ± 4.5	0.279
Left atrium diameter, mm						
Baseline	46.9 ± 6.3	47.0 ± 7.1	0.776	47.1 ± 6.3	46.7 ± 7.0	0.373
Last clinical check-up	46.2 ± 7.4	46.0 ± 7.3	0.819	46.5 ± 7.4	46.2 ± 7.5	0.610
Median follow-up duration, years (IQR)	3.8 (1.5; 7.3)	4.6 (1.6; 8.3)		4.0 (1.6; 7.4)	4.6 (1.7; 8.8)	

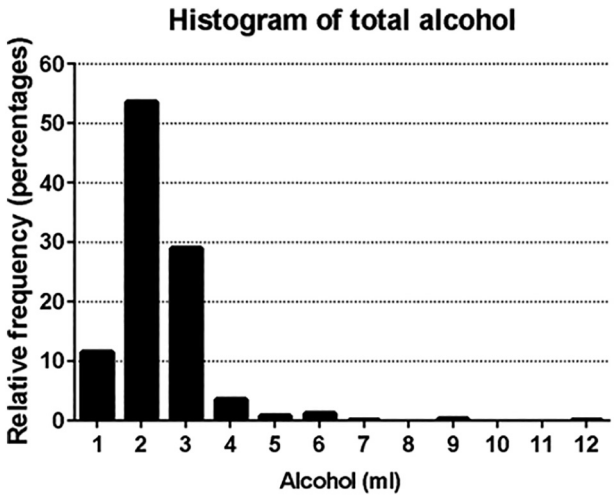

Fig. 1. Histogram of alcohol doses in the whole ASA cohort.

(v) severity of dyspnea (NYHA class); and (vi) rate of reintervention (re-ASA or myectomy).

2.7. Statistical analysis

All data were assessed and edited by experienced research statisticians. Data are presented as means±standard deviations (±SDs), medians and interquartile range (IQR), and numbers and proportions for categorical variables. Mann-Whitney test was used to assess the difference between continuous variables, and the Chi square test between categorical variables. We calculated a propensity score for the following baseline variables: sex, age, LV outflow gradient, LV end-diastolic diameter, basal interventricular septum thickness, LV ejection fraction, NYHA class, implanted ICD or pacemaker. The propensity score was estimated using a logit model. Matching was performed using 1:1 nearest neighbor method without replacement, which yielded 385 patients with the low alcohol dose of 1.0–1.9 mL, who were matched with 385 patients with the high alcohol dose of 2.0–3.8 mL. Cox's proportional hazards model with clustered standard errors was used for the analysis of time to event. To find risk predictors of all-cause mortality, the following baseline variables were evaluated in a univariate model: sex, age, LV outflow gradient, LV end-diastolic diameter, interventricular septum thickness, LV ejection fraction, NYHA class 1 or 2, and NYHA class 3 or 4. Subsequently, a multivariable analysis was performed using a backward stepwise algorithm for Cox's proportional hazards model. Estimates for long-term outcomes were made by the Kaplan–Meier method (including 95% confidence intervals) and differences were assessed by the log rank test. P value <0.05 was considered statistically significant. All reported p values were 2-sided. The software Prism (release 6.05, GraphPad Software Inc.) and SPSS 25.0.0.1 (IBM Corporation 2019) were used for statistical analysis.

3. Results

We included and analyzed a total of 1448 patients with obstructive HCM treated with ASA. In this entire cohort, the mean dose of alcohol administered during ASA was 2.1 ± 0.7 mL (Fig. 1). The correlation between alcohol dose and septal thickness in the whole population was very weak ($r = 0.13$; $p < 0.01$).

We identified 465 (32%) patients treated with the low dose of alcohol (1.0–1.9 mL) and compared these to 983 (68%) patients treated with the high dose of alcohol (2.0–3.8 mL) (unmatched cohorts; Table 1).

The propensity-matched cohort analysis comprised 770 (53%) patients divided into two groups including the low-dose group (alcohol dose 1.0–1.9 mL, $n = 385$ patients) and the high-dose group (alcohol dose 2.0–3.8 mL, $n = 385$ patients) (Table 1). In the matched groups, there were significant differences neither in the baseline rate of implanted pacemakers or ICDs (8% in the low-dose group vs. 8% in the high-dose group; $p = 1$) nor in the preexisting bundle branch blocks (10% in the low-dose group vs. 12% in the high-dose group; $p = 0.42$).

3.1. Short-term results

In the matched cohorts, the 30-day mortality rate was 0.6% (0.8% in the low-dose group vs. 0.5% in the high-dose group; $p = 1$). Causes of death are summarized in Table 2. There were no significant differences in the early occurrences of VT/VF requiring electrical cardioversion or appropriate ICD discharge, cardiac tamponade, or permanent pacemaker implantation, respectively, between the two groups (Table 3).

3.2. Long-term results

No patients were lost to follow-up. In the matched cohorts, the median follow-up duration was 4.5 years (IQR 1.8–8.3 years), and a total of 110 (14%) patients died in the course of 4143 patient-years, representing 2.58 deaths and 2.64 deaths per 100 patient-years in the low-dose and the high-dose group, respectively. The Kaplan-Meier curves of all-cause mortality rates are shown in Fig. 2 with no significant difference between the matched groups (logrank, $p = 0.92$).

In multivariable analysis, the predictors of all-cause mortality were female sex, age >60 years, baseline septum thickness ≥22 mm and baseline LV outflow gradient ≥90 mmHg (Table 4).

In the matched groups, there were no significant differences in the long-term NYHA class and LV outflow gradient (Table 1).

A total of 80 (10%) patients in the matched groups underwent repeated septal reduction therapy because of insufficient symptom relief and residual LV outflow gradient after the initial ASA (48 patients in the low-dose group vs. 32 patients in the high-dose group). The Kaplan-Meier curves presenting septal reduction re-intervention rates are shown in Fig. 3 and the low-dose group experienced significantly more reinterventions (logrank, $p = 0.04$).

Table 2
Causes of deaths during the month after ASA.

Cause	Unmatched cohorts			Matched cohorts		
	Alcohol 1.0–1.9 mL	Alcohol 2.0–3.8 mL	*P* value	Alcohol 1–0-1.9 mL	Alcohol 2.0–3.8 mL	*P* value
	N = 465	*N* = 983		*N* = 385	*N* = 385	
Cardiac tamponade, *n* (%)	1 (0.2)	2 (0.2)	1.000	1 (0.3)	1 (0.3)	1.000
Carcinoma, *n* (%)	1 (0.2)	0	0.321	1 (0.3)	0	1.000
Sudden cardiac death (ventricular fibrillation), *n* (%)	1 (0.2)	1 (0.1)	0.539	0	0	1.000
Pulmonary embolism, *n* (%)	1 (0.2)	1 (0.1)	0.539	1 (0.3)	0	1.000
Stroke, n (%)	0	1 (0.1)	1.000	0	0	1.000
Heart failure, *n* (%)	0	1 (0.1)	1.000	0	1 (0.3)	1.000
Total, *n* (%)	4 (0.9)	6 (0.6)	0.735	3 (0.8)	2 (0.5)	1.000

Table 3
Non-hierarchical occurrence of major cardiovascular adverse events during the first month after ASA.

Event	Unmatched cohorts			Matched cohorts		
	Alcohol 1.0–1.9 mL	Alcohol 2.0–3.8 mL	*P* value	Alcohol 1–0-1.9 mL	Alcohol 2.0–3.8 mL	*P* value
	N = 465	*N* = 983		*N* = 385	*N* = 385	
Defibrillation for VT/VF or appropriate ICD discharge, *n* (%)	9 (1.9)	11 (1.1)	0.232	7 (1.8)	6 (1.6)	1.000
Cardiac tamponade, *n* (%)	8 (1.7)	8 (0.8)	0.175	7 (1.8)	4 (1.0)	0.546
New permanent pacemaker, *n* (%)	50 (10.8)	102 (10.4)	0.854	37 (9.6)	35 (9.1)	0.902
Total, *n* (%)	67 (14.4)	121 (12.3)	0.277	51 (13.2)	45 (11.7)	0.586

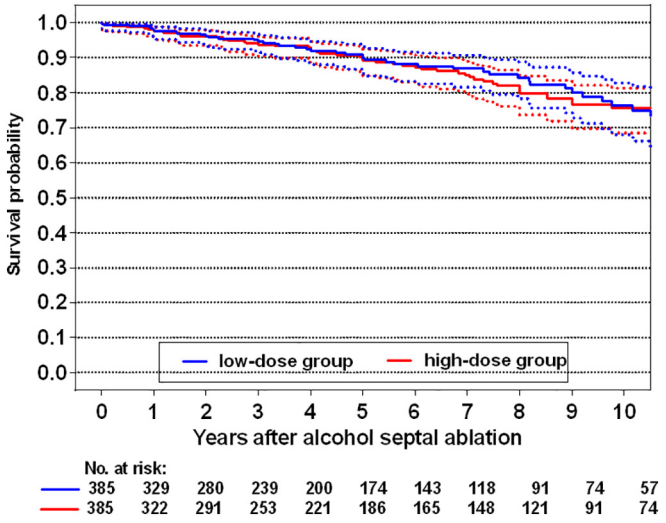

Fig. 2. Central illustration. The Kaplan-Meier curves with 95% confidence intervals for the long-term survival of ASA patients treated with the low-dose (1.0–1.9 mL) or the high-dose (2.0–3.8 mL) of alcohol ($p = 0.92$).

4. Discussion

To the best of our knowledge, this is the largest reported study to compare short- and long-term outcomes of ASA patients treated with low- or high-doses of alcohol. The most important findings of this study were as follows: [1] Propensity-matched patients treated with the low- (1.0–1.9 mL) or the high-dose (2.0–3.8 mL) of alcohol had similar 30-day post-procedural occurrence of major adverse events, including VT/VF requiring electrical defibrillation or appropriate ICD discharge, rate of permanent pacemaker implantation, or occurrence of cardiac tamponade, [2] 30-day all-cause mortality rates were also similar between the two groups. [3] In the long-term follow-up, the matched patients had similar all-cause mortality rates, NYHA classes, and LV outflow pressure gradients, and [4] patients treated with the low dose of alcohol had a higher rate of repeated septal reduction therapy.

Existing evidence of alcohol dose-related outcomes of ASA has been derived from a small single-center randomized study [10,11] and single-center institutional registries [13–16]. Early after the introduction of ASA in the mid-1990s, higher doses (mean dose ≥2.8 mL) of desiccated alcohol were used [12–14]. Later, Kuhn et al. reported the 10-year experience with ASA ($n = 264$) in Germany and compared mid-term outcomes of ASA patients treated in the "low-dose" and "high-dose" eras. These investigators concluded that patients who were given a higher amount of alcohol (>2 mL) had a higher mortality rate than those given lower doses [15]. Subsequently, a small, single-center, prospective, randomized study did not find any differences in hemodynamic effects and long-term survival between patients with low- and high doses of alcohol [10,11]. Similarly, Liebregts et al. retrospectively evaluated patients treated in a non-randomized fashion with low- (≤2 mL) or high-dose (>2 mL) of alcohol ($n = 267$) and found that the long-term survival and rates of adverse arrhythmic events were similar [16]. Even though all these studies and clinical experience from institutional registries led to the widely held view to use lower doses of alcohol to decrease post-ASA complications [17–20], there is still an ongoing debate regarding the appropriate alcohol dose for ASA.

Optimally, the alcohol dose injected during ASA should ensure development of adequate necrosis in the thickened subaortic myocardium, leading to myocardial shrinkage and significant widening of the LV outflow tract. Additionally, the extent of post-ASA myocardial scar tissue should not induce significant arrhythmogenic events or heart failure. It is important to note, however, that apart from the amount of injected alcohol, a range of factors including, for example, anatomy of the septal branches, mechanism of subaortic dynamic obstruction and interplay with the mitral apparatus, papillary muscles abnormalities, magnitude of septal thickness, and septal hypertrophy geometry play important roles in decision-making to tailor optimal therapy for each individual HOCM patient [21–25]. Since these and other unmeasured factors were not taken into account in our study it is impossible to establish a specific alcohol dose suitable for all HOCM patients treated with ASA. However, this study demonstrates that the predominant alcohol doses used for ASA during the last two decades are safe and effective, and the results suggest that for this range of alcohol doses, the specific dose volume plays minor role in the long-term outcomes of ASA patients.

In current clinical practice the principal focus remains on optimal selection of patients suitable for ASA. If ASA is selected as treatment strategy, precise intra-procedural determination of the target septal branch perfusion territory to ensure correct localization of alcohol is more important for long-term procedural success than the precise alcohol dose in the 1.0–3.8 mL range.

In the previous analysis which included 1275 patients treated with alcohol doses ranging between 0.4 and 11 mL we found a relationship

Table 4
Predictors of all-cause mortality ($n = 770$).

	HR (95% CI)	Number of events	*P* value
Females; $n = 418$	1.6 (1.0; 2.6)	81	0.030
Age			
60–69 years; $n = 194$	1.9 (1.1; 3.1)	21	0.017
≥70 years; $n = 179$	3.3 (2.1; 5.4)	47	<0.001
LV septum thickness ≥22, mm; $n = 212$	1.6 (1.1; 2.4)	40	0.023
LV outflow gradient ≥90 mmHg; $n = 224$	1.7 (1.1; 2.5)	22	0.011

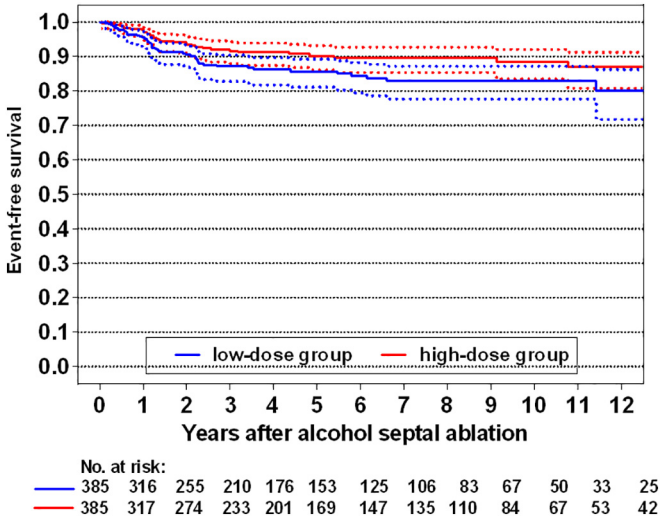

Fig. 3. The Kaplan-Meier curves with 95% confidence intervals for the long-term freedom of repeated septal reduction therapy of ASA patients treated with the low-dose (1.0–1.9 mL) or the high-dose (2.0–3.8 mL) of alcohol ($p = 0.04$).

between alcohol dose and (i) a higher incidence of peri-procedural complete heart block, and (ii) reduction of LV obstruction [8]. However, in the present study we have excluded patients who were treated with either ultra-low (<1 mL) or ultra-high (>3.8 mL) alcohol doses that are currently not used anymore. Consequently, the only significant difference between the propensity-matched ASA groups was an increased need for repeated septal reduction therapies in the patients treated with the low-dose of alcohol. This finding is in line with results of previous studies that demonstrated a positive correlation between alcohol dose and subsequent myocardial biomarker release indicative of the amount of myocardial necrosis [11,26,27]. Thus, from the clinical point of view, an effort to minimize the final post-ASA myocardial scar by using lower doses of alcohol might lead to insufficient tissue ablation and increased need of repeated ASA or myectomy [3,11,28]. Conversely, a more aggressive approach might reduce repeated procedures.

This study has several limitations. First, propensity score-matching has inherent limitations and does not make up for a prospective, randomized, controlled trial. However, results of this study are consistent with the only published randomized study [10,11], which, however, comprised ten times less patients from a single center. Moreover, large randomized trials of alcohol doses for ASA are unlikely to be performed in the near future. Second, some diversity exists in the field with respect to interpretation and implementation of the existing evidence on ASA, e.g. patient selection, myectomy as an alternative invasive strategy, and some differences in ASA technique, that might limit the generalizibility of our results [9,29]. On the other hand, these differences ensured the diversity of interventional techniques used in this international study.

5. Conclusions

Propensity-matched obstructive HCM patients treated with low-dose (1.0–1.9 mL) or high-dose (2.0–3.8 mL) of alcohol during ASA had similar short- and long-term outcomes, except for a higher rate of repeated septal reduction procedures in the group treated with the low-dose of alcohol.

Dislosure

All authors have declared any potential conflicts in the disclosure section of the paper.

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None.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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